Established in 1871

Swiss Medical Weekly

Formerly: Schweizerische Medizinische Wochenschrift

The European Journal of Medical Sciences

Original article | Published 25 October 2013, doi:10.4414/smw.2013.13863

Cite this as: Swiss Med Wkly. 2013;143:w13863

Changes in renal function over time in patients with cardiac resynchronisation therapy

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Abstract

QUESTION UNDER STUDY: Cardiac resynchronisation therapy (CRT) with defibrillator back-up (CRT-D) is widely used in selected patients with moderate/severe heart failure. Renal failure is common in these patients. Data on the impact of CRT on renal function are controversial and limited by short follow-up. The aim of this study was to describe changes in glomerular filtration rate (GFR) from baseline compared with 1 and 2 years after CRT implantation.

METHODS: A total of 284 CRT-D patients with creatinine levels at baseline and after 1 year were identified in two prospective registries. In 149 patients, levels after 2 years were available. GFR in ml/min/1.73 m^2 was estimated with the Modification Diet in Renal Disease equation and patients stratified into GFR stages 1 to 4.

RESULTS: The population was predominantly male (75%), mean (± standard deviation) age was 61 ± 7 years and ejection fraction 24% ± 8 %. GFR was 63 ± 24 ml/min/1.73 m^2 at implantation and 60 ± 24 ml/min/1.73 m^2 after 1 year ($p = 0.26$). At the 2-year follow-up, GFR had decreased from 60 ± 21 to 56 ± 21 ml/min/1.73 m^2 ($p = 0.04$). Mean GFR decreased in stages 1 and 2, remained stable in stage 3 and improved in stage 4 patients. After 2 years, GFR had decreased ≥10 ml/min/1.73 m^2 in 42%, but improved in only 15% ($p = 0.04$).

CONCLUSIONS: Overall, mean GFR in CRT-D patients decreases at 1 and 2 years after implantation, depending in part on the initial degree of renal function. However, the chance of further substantial deterioration (≥10 ml/min/1.73 m^2) is considerable.

Key words: *cardiac resynchronisation therapy; defibrillators; glomerular filtration rate*

Introduction

In selected patients with drug refractory heart failure, cardiac resynchronisation therapy (CRT) without or with a defibrillator (CRT-D) has been shown to reduce both mortality and morbidity [1–4] and is now a recommended therapeutic option for patients with moderate to severe heart failure and wide QRS complex [5]. Renal failure is a common co-morbidity in heart failure patients [6–8] and has also been recognised as an independent risk factor for morbidity and mortality in these patients [9, 10]. Renal failure is also common in CRT patients [3, 11] where it has been shown to be an independent predictor of mortality [10]. Decreased cardiac output and venous congestion as measured by right heart catheterisation have been proposed as possible pathophysiological mechanisms [12]. Advancing renal failure has been shown to be associated with a widening of the QRS complex [6]. As CRT reduces forward failure and improves cardiac output, it might also lead to an improvement in renal function. Current data are controversial and limited by a short follow-up [11, 13]. Therefore, the aims of this study were: a) to determine changes in renal function over a period of at least one year after implantation, if possible after two years and b) to assess this in different stages of renal failure.

Methods

The patients of the present study stemmed from the prospective ICD registries of the Cardiology departments of the University of Basel Hospital, Switzerland and of Erasmus MC in Rotterdam, the Netherlands. The registry in Basel was started on the 1st of July 1999 and covers a large part of North-Western Switzerland. The registry in Rotterdam was started on the 1st of October 1998 and covers a large area around Rotterdam. They encompassed per end of September 2009, 777 and 1574 patients respectively. Out of these registries, all patients in whom a CRT-D was implanted were identified. Patients were included in the study if serum creatinine levels at baseline and at least after one year were available. We excluded 18 patients who had no creatinine level available at baseline and/or after 1 year (13 and 5 patients). In a subset of patients, creatinine levels after 2 years of follow-up were also available. The CRT-D was implanted according to local practice in the two centres with conscious sedation and mostly dual-coil/passive ICD leads in Basel and single-coil/active ICD leads in Rotter-

dam. All clinical diagnosis (e.g., coronary artery disease or diabetes) were taken from the patient chart.

GFR was estimated via an internet based calculator [14] using the abbreviated Modification of Diet in Renal Disease (MDRD) equation [15]. This model was used for its simplicity and wide availability, even though it might overestimate renal function [16]. The creatinine levels used for calculation were always the last ones determined *before* CRT-D implantation (usually the day before) and never taken after the procedure, as contrast agents used for coronary sinus venography may have an immediate impact on renal function. Patients were then stratified into one of 4 GFR stages [17]: Chronic kidney disease (CKD) stage 1 with a normal kidney function (i.e., a GFR ≥90 ml/min/1.73 m^2); CKD stage 2 with a mild decrease in kidney function (i.e., a GFR from 60–89 ml/min/1.73 m^2); CKD stage 3 with a moderate decrease in kidney function (i.e., a GFR from 30–59 ml/min/1.73 m^2) and CKD stage 4 with a severe decrease in kidney function (i.e., a GFR <30 ml/min/1.73 m^2). In order to differentiate between clinically important changes in GFR and mere incidental changes in stages (i.e., a decrease from 61 to 59 ml/min/1.73 m^2 is a change in stage based on the definition, but obviously not clinically relevant), we empirically defined a change of ≥ ± 10 ml/min/1.73 m^2 as "relevant" and determined these changes as well. Multivariate analyses were performed to determine predictors for a "relevant" improvement or impairment of GFR as defined above. Creatinine levels used for the follow-up determination of GFR were those closest to the time point one and two years after CRT implantation.

Statistics

Continuous data are expressed as mean values (± one standard deviation [SD]). The chi-square test or Fisher's test were used to compare categorical data. Comparisons of all continuous variables were calculated using an unpaired two-sided student's t-test. Univariate and multivariate analysis with logistic regression were used to examine the association between baseline clinical characteristics and changes in GFR during follow-up. Characteristics entered in the multivariate analysis included NYHA class, LV-ejection fraction, QRS width, hypertension, diabetes, diurectics use, ACE/ARB use and CKD stage 3 or 4. Analyses were done using SPSS version 16.

Results

The study cohort consisted of 284 patients (165 from Rotterdam, 119 from Basel). The population was predominantly male (75%) with a mean age of 61 years (SD 7; range 12–82). Ischaemic and non-ischaemic cardiomyopathy were almost equally distributed, mean LVEF was 24 % (SD 8). Heart failure drug therapy was on an optimal level with virtually all patients taking ACE-inhibitors or angiotensin receptor antagonists. The CRT-D was implanted for primary prevention in 76% of cases. Baseline characteristics are shown in table 1.

GFR values were available in all 284 patients at baseline and after 1 year of follow-up, and in 149 (52%) patients after 2 years of follow-up. GFR at baseline was 62.8 ± 24.3 ml/min/1.73 m^2 and 60.3 ± 23.6 ml/min/1.73 m^2 after one year (p = 0.26). In the 149 patients with 2 years of follow-up GFR decreased from 59.7 ± 21.4 ml/min/1.73 m^2 to 55.5±21.5 ml/min/1.73 m^2 (p = 0.004).

At baseline, moderate to severe impairment in renal function (i.e. CKD stage 3 or 4) was present in 50% (143/284) of the patients. This percentage had not changed after 1 year (150/284; 52.8%) or after 2 years (83/149; 55.7%).

Table 1: Baseline characteristics of the 284 patients.

	Overall cohort	Basel cohort	Rotterdam cohort	p-value
Age	61 years (SD 7)	63 years (SD 10)	59 years (SD 12)	0.005
Male gender	214 (75%)	101 (85%)	113 (68%)	0.002
ICD indication				
Primary prevention	215 (76%)	88 (74%)	127 (77%)	0.58
Ischaemic cardiomyopathy	131 (46%)	51 (43%)	80 (48%)	0.40
With CABG *	67 (51%)	27 (53%)	42 (52%)	1.00
Ejection fraction (n = 254)	24% (SD 8%)	24% (SD 7%)	24% (SD 7%)	0.63
NYHA class	2.75 (SD 0.49)	2.76 (SD 0.53)	2.73 (SD 0.46)	0.60
II	79 (28%)	34 (29%)	45 (27%)	
III	198 (70%)	79 (66%)	119 (72%)	
IV	7 (2%)	6 (5%)	1 (1%)	
Sinus rhythm	207 (73%)	106 (89%)	101 (61%)	0.0001
Hypertension	119 (42%)	73 (61%)	46 (28%)	0.0001
Diabetes	77 (27%)	30 (25%)	47 (28%)	0.6
QRS width	164 ms (SD 27 ms)	161 ms (SD 31 ms)	167 ms (SD 30 ms)	0.14
Drug therapy at inclusion				
ACE inhibitors/ARBs	273 (96%)	115 (97%	158 (96%)	0.77
Diuretics	249 (88%)	109 (92%)	140 (85%)	0.1
Beta-blockers	222 (78%)	96 (81%)	126 (76%)	0.47
Amiodarone	74 (26%)	33 (28%)	40 (24%)	0.58
CKD † stage 1	46 (16%)	21 (18%)	25 (15%)	
CKD stage 2	95 (33%)	38 (32%)	57 (34%)	
CKD stage 3	124 (44%)	52 (44%)	72 (44%)	
CKD stage 4	19 (7%)	8 (7%)	11 (7%)	

* Coronary artery bypass graft; † Chronic kidney disease

Mean GFR of patients in CKD stages 1 and 2 (i.e., those with a normal or near-normal renal function) decreased, remained stable in stage 3 and improved in stage 4, especially after a follow-up of 2 years (for details see table 2).

Changes in GFR of ≥10 ml/min/1.73 m^2 were observed in 134/284 patients after 1 year (decrease in GFR of ≥10 ml/min/1.73 m^2 in 30%, increase of ≥10 ml/min/1.73 m^2 in 17%, p-p-valuevalue 0.19). After 2 years, GFR had decreased for ≥10 ml/min/1.73 m^2 in 42%, and improved in only 15% (p-value 0.04). Patients in CKD stages 3 and 4 increased their GFR for >10 ml/min/1.73 m^2 more often than those in stage 1 and 2 (p value 0.0001 after 1 and 2 years). However, because in CKD stages 3 and 4 a similar rate of patients (20%–25%) exhibited an increase or a further decrease of ≥10 ml/min/1.73 $m^{2,}$ respectively, the effect of CRT on renal function based on baseline GFR and/or CKD stage is not predictable. Details of changes in the different stages are shown in table 3.

During follow-up of 45 ± 9 months, 68 patients (24%) died. There were differences in GFR both at baseline and after 1 and 2 years of follow-up between survivors and nonsurvivors (56 ± 24 ml/min/1.73 m^2 in dead vs 65 ± 24 ml/min/1.73 m^2 in surviving patients at baseline; 53 ± 24 ml/min/1.73 m^2 vs 62 ± 23 ml/min/1.73 m^2 after 1 year; 43 ± 21 ml/min/1.73 m^2 vs 59 ± 20 ml/min/1.73 m^2 after 2 years (p-values 0.008, 0.005 and 0.0001)). Mortality was 17% in CKD stage 1, 15% in stage 2, 31% in stage 3 and 42% in stage 4 (p-value 0.007), and 16% in GFR >60 ml/min/1.73 m^2 or 32% in GFR <60 ml/min/1.73 m^2. Mortality was similar in patients with a decrease in GFR of >10 ml/min/1.73 m^2 as compared to patients with improved or stable GFR (29.4% vs 25.0% vs 20.5%). ICD therapies were delivered in 107 patients (38%). There was no association between ICD therapy and the different CKD stages (p-value 0.35).

In the univariate analysis, only age (OR per year 0.977 [CI 0.957–0.997] p-value 0.028) and CKD stage 3 and 4 (OR 0.338 [CI 0.123–0.930] p-value 0.036) were negative predictors for an improvement of GFR >10 ml/min/1.73 m^2 after 1 year. In the multivariate analysis only baseline CKD stage 3 and 4 (OR 0.339 [CI 0.123–0.933] p-value 0.036) remained in the model. Considering an impairment of GFR > 10 ml/min/1.73 m^2 after 1 year, QRS width was the only significant covariate in univariate analysis (OR per ms 0.990 [CI 0.983-0.997] p-value 0.005).

In a separate analysis we compared the 77 patients (27%) with diabetes to the 207 nondiabetic patients. Both at implantation and after 1 year of follow-up, diabetic patients were in a higher CKD stage (p-values 0.009 and 0.05, respectively) and had lower mean GFR values, but exhibited a similar decline in GFR (tables 4 and 5). The same shifts in GFR as in nondiabetics were seen according to CKD stages (1 – 10 ml, 2 – 8 ml, 3 – 1 ml, 4+ 10 ml). Due to the small number (n = 38), no analysis was performed after 2 years.

Table 2: Changes of mean glomerular filtration rate (GFR) according to baseline CKD stage after 1 and 2 years.

	n	Baseline GFR	GFR after 1 year	p-value
Overall	284	62.8 ± 24.3	60.3 ± 23.6	0.26
Baseline CKD † stage 1	46 (16%)	101.9 ± 13.8	87.5 ± 23.2	0.0005
Baseline CKD stage 2	95 (33%)	73.0 ± 8.0	69.6 ± 14.6	0.04
Baseline CKD stage 1+2	141 (50%)	82.5 ± 17.0	75.5 ± 19.7	0.002
Baseline CKD stage 3	124 (44%)	46.6 ± 7.9	47.4 ± 15.8	0.62
Baseline CKD stage 4	19 (7%)	22.5 ± 5.0	31.8 ± 14.0	0.01
Baseline CKD stage 3+4	143 (50%)	43.4 ± 11.1	45.3 ± 16.4	0.25
		Baseline GFR	**GFR after 2 years**	**p-value**
Overall	149	59.7 ± 21.4	55.5 ± 21.4	0.04
Baseline CKD stage 1	24 (16%)	99.5 ± 9.8	74.6 ± 20.1	0.0001
Baseline CKD stage 2	50 (33%)	73.6 ± 8.3	62.3 ± 19.2	0.0002
Baseline CKD stage 1+2	74 (50%)	82.0 ± 15.0	66.3 ± 20.3	0.0001
Baseline CKD stage 3	65 (44%)	47.4 ± 7.5	47.3 ± 16.6	1
Baseline CKD stage 4	10 (7%)	24.1 ± 4.3	29.6 ± 9.4	0.1
Baseline CKD stage 3+4	75 (50%)	44.3 ± 10.8	45.0 ± 17.0	0.78

† Chronic kidney disease

Table 3: Changes in glomerular filtration rate according to baseline CKD stage after 1 and 2 years.

	n	Increase in GFR ≥10	Decrease in GFR ≥10
After 1 year:			
Overall	284	49 (17%)	85 (30%)
Baseline CKD † stage 1	46	3 (7%)	28 (61%)
Baseline CKD stage 2	95	14 (15%)	31 (33%)
Baseline CKD stage 3	124	25 (20%)	26 (21%)
Baseline CKD stage 4	19	7 (37%)	0 (0%)
After 2 years:			
Overall	149	22 (15%)	63 (42%)
Baseline CKD stage 1	24	0 (0%)	21 (87%)
Baseline CKD stage 2	50	4 (8%)	24 (48%)
Baseline CKD stage 3	65	15 (23%)	18 (28%)
Baseline CKD stage 4	10	3 (30%)	0 (0%)

† Chronic kidney disease

Discussion

Main findings of this study

At implantation, 50% of CRT patients had a moderate to severe reduction in renal function. After 2 years, mean GFR declined further. An impaired renal function conveys a worse prognosis. While patients with a normal or mildly reduced GFR exhibited a significant decrease in GFR during mid-term follow-up, patients with severely impaired GFR improved, but their mean GFR was still <30 ml/min/1.73 m^2.

In a contemporary heart failure population, 40%–50% of patients present with a GFR of <60 ml, regardless of whether they are seen in an outpatient setting [6], or whether they are implanted with an ICD [17] or a CRT-D [3, 10, 18, 19]. 5%–8% of patients had a GFR of <30 ml ml/min/1.73 m^2, often heading towards haemodialysis. In this setting, it is important to know if CRT can affect this course as it was shown that an ICD offers no benefit in patients with severely impaired renal function [20].

Evolution of GFR over time

Current literature related to the evolution of GFR in CRT patients is small and limited by a short follow-up period of 3 to 6 months [11, 13, 19, 21], methodological problems [14], a main focus on mortality [22] or a vague definition of CKD stages [20, 21]. In the present study, all 284 patients had GFR estimations at 1 year follow-up and also almost 50% after 2 years. By combining the literature on short-term follow-up [11, 18, 21, 22] with our data, we tried to speculate on the evolution of GFR over a period of 2 years. Mean GFR decreases slightly (0–2 ml) after 3 to 6 months and this decrease continues after one and two years (–2.5 ml and –4 ml). However, there are major differences according to baseline renal function. In patients with baseline GFR >60 ml/min/1.73 m^2, GFR decreases between 2 and 10 ml/min/1.73 m^2 after 3 to 6 months and the decrease continues further (–7 ml and –16 ml, respectively). In patients with baseline GFR <60 ml/min/1.73 m^2, the opposite effect is seen. GFR initially improves by 1–8 ml/min/1.73 m^2, but goes back to baseline after 1 and 2 years. In patients with GFR <30 ml/min/1.73 m^2, the initial improvement of 3–8 ml/min/1.73 m^2 is preserved after 1 and 2 years.

CKD stages are somehow arbitrary. We therefore introduced an empirically chosen level of "change of ±10 ml/min/1.73 m^2" to overcome this. Our analysis demonstrated that the higher the initial CKD stages were, the more patients showed an increase of >10 ml/min/1.73 m^2 of GFR after 1 and 2 years and the other way round. There was a continuous rise of this percentage up to 37% in CKD stage 4. This could be used as a strong argument in favour of CRT use even in patients with poor renal function. However, changes seem unpredictable. The analysis based on individual patient's GFR demonstrates that a similar rate (20%–25%) show a substantial change in either direction. Thus, a recommendation cannot be given to implant a CRT-D in a patient with advanced renal failure in hope for substantial improvement of GFR nor to withhold it applying the argument that renal function will further decrease and the patient not draw benefit from the device. However, due to the competing risk of severe renal failure [20], use of a CRT-pacemaker instead of a CRT-defibrillator should be discussed with such patients, as here the main goal in them might be the reduction in morbidity (primarily less hospitalisations for heart failure) and not a reduction in mortality.

Response to CRT

As no standardised follow-up programme including serial echocardiography was performed, we cannot correlate "response" and GFR changes, which is a limitation of this study. Data on such a correlation are scarce. In a small study (85 patients, follow-up 3 months), patients who "responded" (i.e. a reduction of 10% in end-systolic volume of the left ventricle (LVESV)) had a rise of GFR of mean 2 ml, whereas GFR dropped a mean of 13ml in "non-responders" [13]. A less pronounced difference was seen in a subgroup of 133 patients published by van Bommel et al. [21]. "Response" was defined as a reduction in LVESV of >15%. After 6 months, GFR remained stable in "responders" (–0.6 ml), whereas it dropped in "nonresponders" (–4.7 ml, p <0.05). The major limitation of both studies is their very short follow-up, and no other long-term data have been presented so far.

Explanations for the findings of this study and limitations

It seems that in patients with advanced renal failure, some improve GFR due to better organ perfusion, whereas in others the damage is already fixed (i.e., significant interstitial fibrosis, tubular atrophy and glomerulosclerosis) and even with better perfusion no improvement is possible.

Table 4: Absolute values of glomerular filtration rate (GFR) in diabetic (n = 77) vs nondiabetic (n = 207) patients after 1 and 2 years; changes of GFR after 1 year in diabetics according to baseline CKD stage.

	Diabetic	Nondiabetic	p-value
GFR baseline	58 ± 25	65 ± 24	0.05
GFR at 1 year	55 ± 24	62 ± 23	0.04
GFR at 2 years	49 ± 21	58 ± 21	0.04

Table 5: p-values in diabetic patients 0.5 between baseline and 1 year, 0.06 between baseline and 2 years; in nondiabetic patients 0.3 between baseline and 1 year, 0.01 between baseline and 2 years.

	n	At baseline	After 1 year	p-value
Baseline CKD † stage 1	12	99.8 ± 8.6	89.6 ± 17.2	0.08
Baseline CKD stage 2	19	72.9 ± 7.7	65.0 ± 16.4	0.06
Baseline CKD stage 3	35	46.7 ± 8.5	45.6 ± 15.8	0.7
Baseline CKD stage 4	11	22.9 ± 5.0	33.4 ± 16.6	0.06

† Chronic kidney disease

However, this explanation has the above-mentioned limitation: that we have no data on individual "response". The decrease in kidney function within 2 years in CKD stage 1 and 2 patients might not be a sign of ongoing structural kidney damage but be the result of a lower glomerular filtration pressure by rigorous antihypertensive treatment (e.g., ACE inhibitors, angiotensin receptor antagonists). Unfortunately we have no information about whether dosages of ACE inhibitors, angiotensin receptor antagonists or diuretics were increased in these patients in particular. This is another limitation of the study. In addition, no contemporary data are available in the literature of a similar patient group without CRT. Thus it might be that patients without CRT experience a much larger change in renal function and that CRT at least prevents severe impairment.

Conclusions

Half of CRT patients have impaired renal function at implantation. Overall, mean GFR decreases significantly after 1 and 2 years. Changes are dependent on baseline CKD stage. While patients with normal GFR at baseline show a decrease in GFR, those with very poor GFR experience a considerable improvement over time. However, evolution of GFR on an individual basis cannot be predicted, meaning that poor renal function alone should not be used as an argument against CRT. Further research is necessary, with an even longer follow-up period and a special focus on different definitions of response and its impact on renal function.

Funding / potential competing interests: For this survey no funding has been raised. Lara Hitz, Mischa Kühne, Michael Dickenmann: nothing to declare Beat Schaer: speaker's bureau for Medtronic Christian Sticherling: research support and speaker's bureau: Medtronic, Sorin, Biotronik, Boston Scientific Luc Jordaens: research grant and speaker's fee: Biotronik, Boston Scientific, Medtronic, St. Jude Medical, Sorin Stefan Osswald: research support by Medtronic, St. Jude Medical, Biotronik, Boston Scientific Dominic Theuns: research grant: Biotronik, St. Jude Medical

Authors' contribution: BS and LH: Both authors contributed equally to this paper.

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